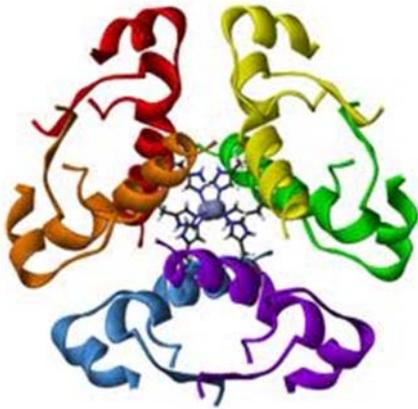




RECOMBINANT



Aretaeus was the most renowned physician of the ancient world, following in the path of Hippocrates, who lived 400 years earlier. Aretaeus' treatise on diseases, which survives to this day, is a remarkably comprehensive catalog of known diseases in perceptive detail. One illness, in particular, was described as fluids being pulled out of the body. Aretaeus named this disease "siphon," or, in its original Greek, diabetes.

Diabetes is a debilitating disease. Symptoms include blurred vision, excessive thirst, frequent urination and fatigue. It is always fatal. In the 2,000 years following Aretaeus, little was known about its causes. Over time, doctors observed that sugar worsened the condition and, by the 19th century, autopsies revealed that diabetics all had a damaged pancreas. It was known that the pancreas supplied digestive juices, but in 1869 a German medical student, Paul Langerhans, observed very small clusters of cells, less than one percent, in the pancreas that seemed to serve no purpose. Twenty years later, two

German physicians, experimenting with dogs, showed that removing the pancreas caused diabetes. They then demonstrated that leaving the pancreas in the body but ligating its tubes to the intestines halted the flow of digestive juices but did not lead to diabetes. So, somehow, in some way, the pancreas was the key to regulating this terrible illness.

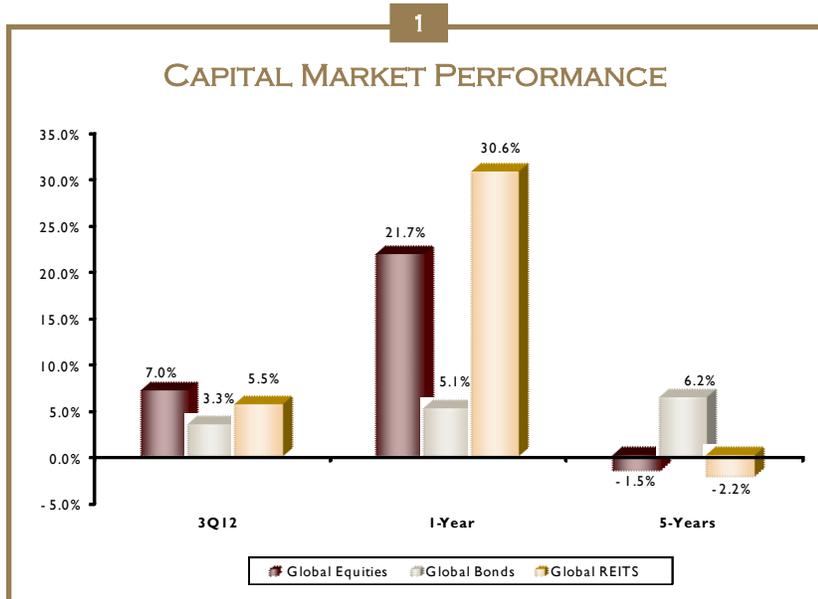
In 1921, Frederick Banting was a surgeon in Toronto with an idea that the pancreatic digestive juices interfered with this other secretion that influenced diabetes. He approached the head of research at the University of Toronto with his idea and asked for lab space to conduct experiments on dogs. Banting was told his theory was wrong, but he was persistent, and eventually received a small desk and 10 dogs. Banting removed the pancreas of one dog, thereby inducing the symptoms of diabetes. On a second dog he tied the ducts that nourished the pancreas, causing it to degenerate. He then removed the organ, froze it, ground it into a powder and then injected this extraction into the first dog. Almost immediately, the symptoms of diabetes disappeared.

Additional experiments on dogs all proved successful, and in January 1922, 14-year old Leonard Thompson was brought to Dr. Banting with advanced diabetes, days away from certain death. He was the first human to receive this injection of a dog's pancreatic hormone, which Banting termed insulin, and within hours, Leonard Thompson's symptoms all disappeared. As he continued to receive these injections, his diabetes remained under control. As more humans received this treatment, all saw their symptoms





“Money makes the world go around...”



abate, and word spread. So important was this breakthrough, the following year Frederick Banting was awarded the Nobel Prize in Physiology (Medicine).

Demand (not surprisingly) for insulin injections soon outstripped supply. Given their close similarity with human insulin, bovine and porcine insulin soon became the principal sources of supply. But about ten percent

of people’s immune systems reject this foreign substance, and longer-term, the production of animal-based insulin was projected to decline even as demand increased.

An alternative to animal-based insulin would be needed, but a breakthrough would have to wait nearly 60 years for a precocious boy from San Bernardino to change the world. He did it by connecting (literally) different chemical pieces together to re-assemble a puzzle.

This approach of deconstruction and re-assembly led to one of the most important medical advances in history, changing the lives of hundreds of millions of people.



Courtesy: BofA Merrill Lynch

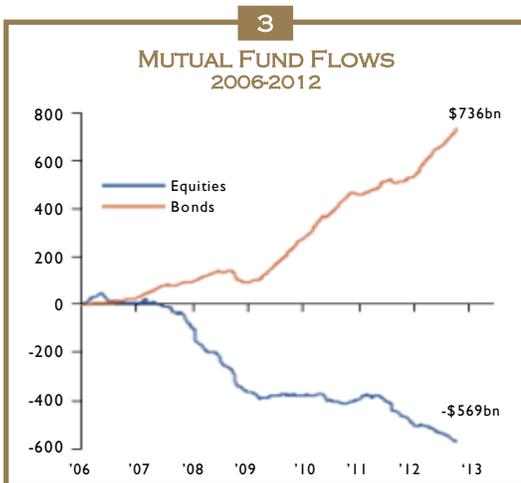
Source: Bloomberg Data as of 04/17/2012

Money makes the world go ‘round’, at least the financial world, and at least this past quarter. Pump-priming by central banks around the globe boosted most capital markets. Egyptian equities were the star, rising 23% last quarter and up 62% so far in 2012. Ireland and Japan sat out the party with modest (-2%) declines in the quarter, while this year the losers have been paced by Greece (-22%) and Argentina (-49%). Commodity prices also jumped in the quarter, led by oil and natural gas, each up about 15%. Precious metals were strong too, perhaps on fears of the diminishing value of all this paper currency sloshing around. Gold rose 10% and silver spiked 25% last quarter.

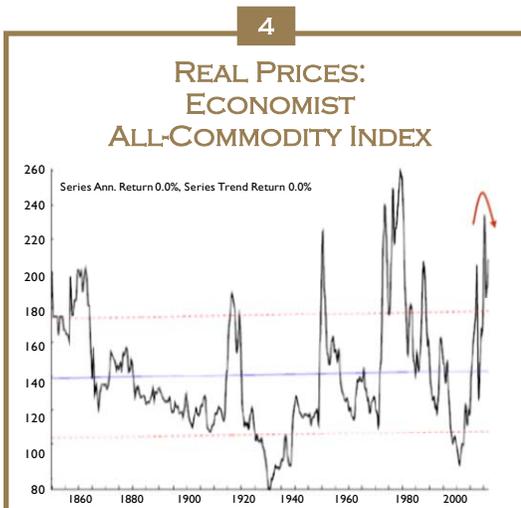
¹ sang the cast of Cabaret.



With these strong moves, a long-term perspective is in order. Following the worst decade for equity investors since the 1930s, returns have rebounded strongly (Chart 2, page 2), even as investors have shifted out of equities and into bonds (Chart 3). Over time, equities have generated positive real returns, whereas commodities have certainly had strong runs for years at a time, but over 150 years have shown a zero real return (Chart 4).



Source: BofA Merrill Lynch Global Equity Strategy, EPFR Global
Courtesy: BofA Merrill Lynch



Source: Global Financial Data, Global Insight, The Economist, MSIM Global Asset Allocation Team analysis. Data as of October 10, 2012.

*Follow the money*² is a useful guide to the capital markets, perhaps even more so today as markets are influenced more by monetary policies than by “real” economic events. In the past four years, the monetary base³ has more than doubled, equity markets have also more than doubled from their lows, yet US GDP has grown a mere 12%⁴. Central bank liquidity has spurred the capital markets higher, but not the broad economy.

The reason is that central bankers have only partial influence on GDP growth. The great American economist of the 1920s, Irving Fisher, expressed GDP growth as a function of money (M) times the velocity of money (V, or how many times a dollar is exchanged, or turned-over).⁵ Central banks can somewhat control the *amount* of money in an economy⁶, but they cannot control the *velocity* of money⁷, which is tied to economic activity and the demand for (and supply of) credit. So, the Fed has created a massive increase in bank reserves, but private sector credit is still contracting, no surprise following the explosion of consumer credit over the past three decades (Chart 5, page 4). These reserves have not made it into the

² *All the President's Men*, Bob Woodward and Carl Bernstein, in a different context of uncovering the Watergate scandal.

³ The sum of currency in circulation plus deposits held at the Federal Reserve.

⁴ All in nominal terms: From October 2008-October 2012, the monetary base rose from \$950 billion to \$2.6 trillion, the S&P 500 rose from 896 (666 at the March 2009 bottom) to 1412, and GDP rose from \$14.0817 trillion to \$15.7757 trillion.

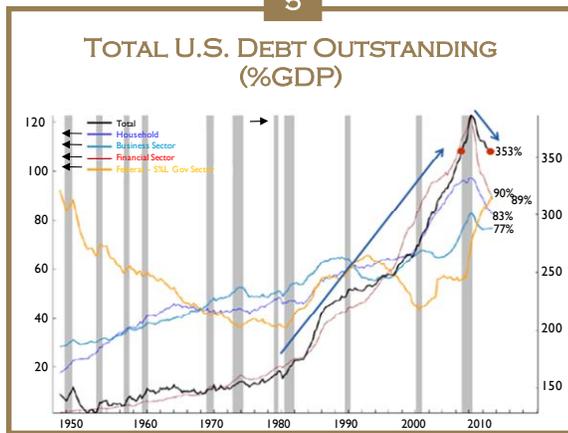
⁵ Fisher called this the equation of exchange: Nominal GDP = M*V.

⁶ Specifically, the Fed mostly controls the monetary base, which is mostly comprised of bank reserves on deposit, but the money *supply* depends on the monetary base times the money multiplier, which is determined by lending decisions of the banks and the public's demand for credit.

⁷ V=GDP/M.



5



Source: DataStream, MSIM Global Asset Allocation Team analysis. Data as of September 27, 2012

economy because the velocity of money is at record lows (Chart 6).

Monetary policies have helped boost the (nominal) values of financial assets, and have similarly impacted commodity prices. Most importantly for consumers, oil has more than doubled from its 2009 lows (from about \$40/barrel to near \$90 today), and gasoline has moved from under \$2/gallon to around \$4. For households where wages have been stagnant for years, the rising cost of energy (and food) is painful.

Accommodative monetary policies are a necessary component to the multi-year repair process of deleveraging, but these policies have secondary consequences: in the near-term, by raising the cost of food and energy, and possibly longer term in the eventual unwinding of this excess liquidity. What is really needed is stronger growth. But that goal seems distant.

Growth is slowing across the globe, from 5% in 2010 to 3.8% in 2011, to 3.3% expected this year. A more dramatic drop has been seen in world trade, which grew 14% in 2010, 5% in 2011 and will be around 2.5% in

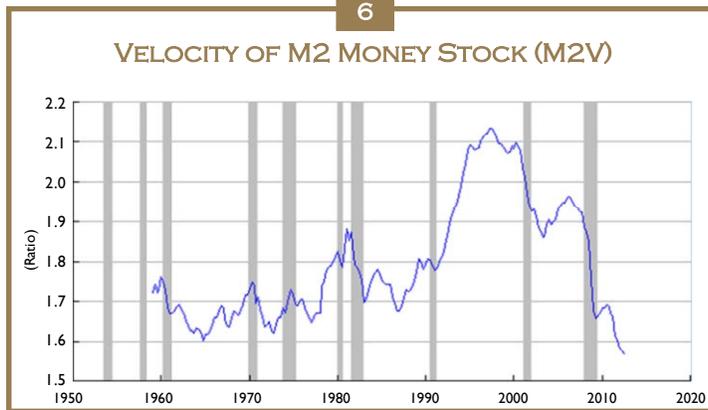
2012 (Chart 7). The IMF sees just 1.5% growth in advanced countries next year and 5.6% growth in developing economies, and pegs the risk of recession at 15% in the US, 25% in Japan and 80% in Europe.

The US is the best house in this struggling neighborhood. Real GDP is growing at around 2% p.a., about its average over the past two years. Barring policy mistakes (which may be a poor assumption), this pace is expected in 2013 as well.

There were some shifts in the composition of growth in the third quarter, with consumer spending and housing providing a lift

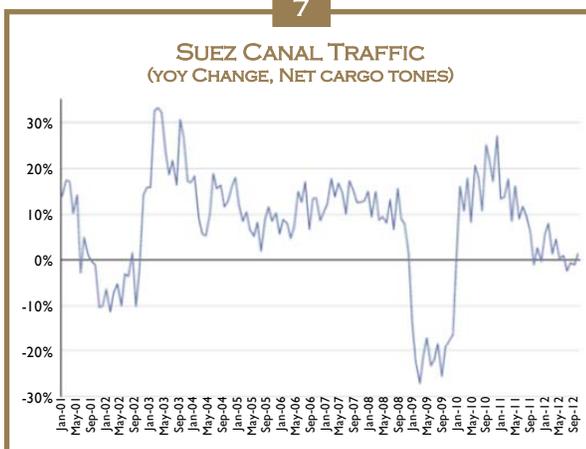
“The US is the best house in this struggling neighborhood ...”

6



Source: Federal Reserve Bank of St. Louis
Shaded areas indicate US recessions.
2012 research.stlouisfed.org

7



Source: Suez Canal Authority

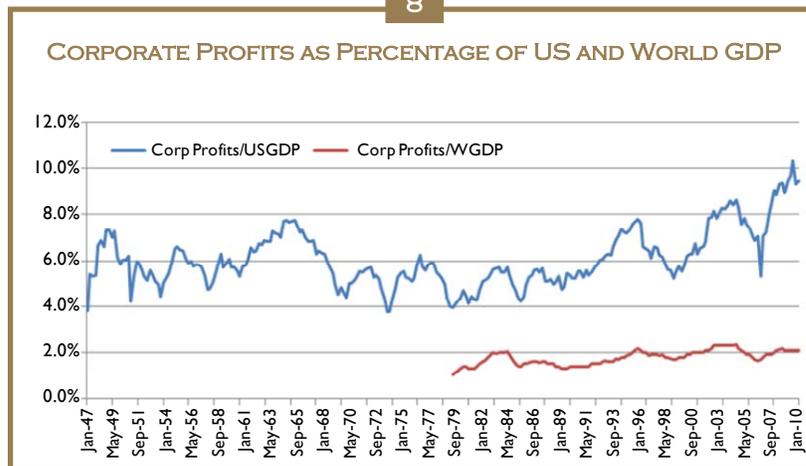


while businesses re-trenched. Retail sales are up more than 5% over the past year, and both home sales and prices are 11% higher than a year ago. Housing inventory fell to 5.9 months, the lowest in seven years and close to record lows. Consumer spending should moderate to be more in-line with (weak) income growth (reduced savings has been the principal source of spending recently), although debt service is now as affordable as anytime in the past 30 years, at just 10.7% of income, helped by low interest rates and modest deleveraging. Housing should continue to be strong in the coming years as supply/demand balances have now shifted significantly.

Businesses have pulled back from an already weak spending pattern. Core durable goods orders fell in each of the last three months, and growth in the capital stock is running at the slowest pace since records began in the 1960s. This is especially surprising since corporate profits are at record levels, around 10% of GDP. But viewed in the context of world GDP, perhaps appropriate as companies have become more global, profits have been modest (Chart 8), and corporations may not feel so flushed.

Employment gains have been steady, but also well below previous cycles (Chart 9). The

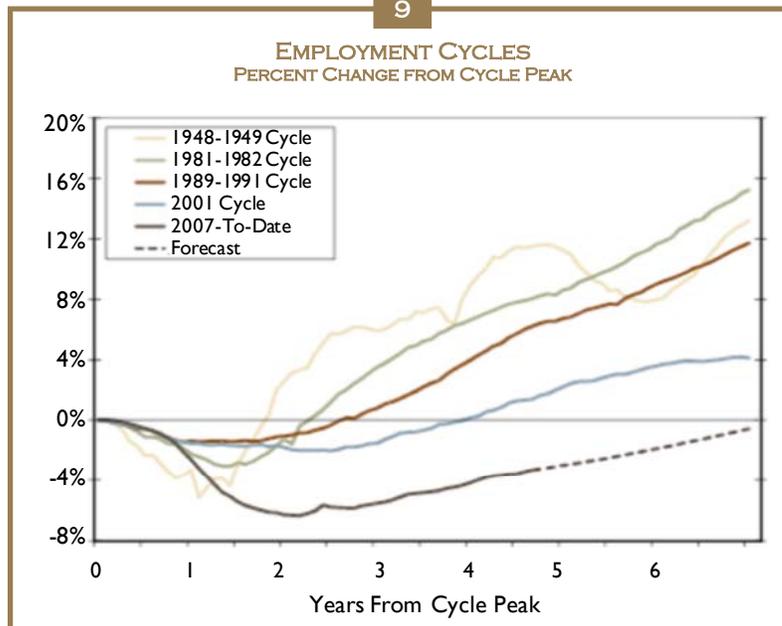
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Source: Bureau of Economic Analysis, IMF

“There were some shifts in the composition of growth in the third quarter...”

9



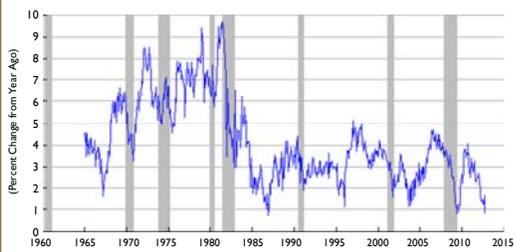
Source: US Department of Labor.

broadest measure of unemployment (the U6 report capturing unemployed and marginally attached workers) hovers near 15%. The median duration of unemployment is 20 weeks with the average duration at 40 weeks. Both are well above any previous cycle, and the gap between the median and



10

AVERAGE WEEKLY EARNINGS OF PRODUCTION AND NONSUPERVISORY EMPLOYEES: TOTAL PRIVATE



Shaded areas indicate US recessions.
Source: U.S. Department of Labor: Bureau of Labor Statistics
2012 research.stlouisfed.org

average suggests there is a large number of unemployed for much longer than 40 weeks. And those who are employed have seen very little growth in weekly earnings (around 1%—Chart 10).

Slowly, the US economy is healing, but the recovery is precarious with a low tolerance for policy errors. Unfortunately, such an event looms near. The failure of Congress and the President to reach a sustainable budget accord last year resulted in a stop-gap compromise that will hike taxes and slash spending by as much as \$750 billion, nearly 5% of GDP, on January 1st. It doesn't take advanced math to figure the effect on an economy growing at 2% if 5% of GDP is subtracted. Most investors assume an agreement will be reached by the lame-duck Congress to forestall this disaster. Let's hope they're right.

Longer term, economic growth is a function of productivity gains plus population change, and there is good reason to expect that trend growth will be lower in the coming decades than in the previous ones. Productivity grew around 2.5% in the 1950s and 1960s, but is currently around 1%. Over the past 50 years, the US workforce grew 1.3% p.a., but 0.5% of this came from women entering the labor pool. Over the coming decades the US workforce is expected to increase only fractionally. This aging of the population is not unique to the US, and is expected to be even more pronounced in most other countries (Table 1). The very low growth rates over the last few years were a result of many factors, principally, the consequences of massive deleveraging in the developed world following the debt bubble. But structural forces may limit growth potential in the future, making the fitful progress of the past few years prologue to the coming decades.

A lower potential growth rate has many implications, including the viability of social welfare programs built on contributions

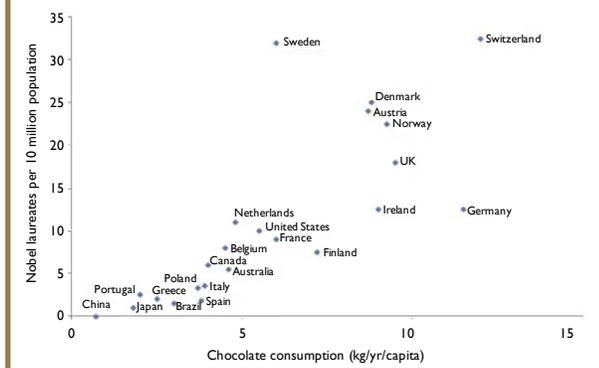
“Slowly, the US economy is healing, but the recovery is precarious...”

TABLE 1
LABOR GROWTH IN SELECTED COUNTRIES

Country	Labor Growth Last 50 Years	Labor Growth Next Decade
USA	1.3%	0.3%
UK	0.4%	0.2%
Europe	0.6%	-0.2%
Japan	0.6%	-0.9%
China	2.0%	0.0%
Brazil	2.5%	0.9%
India	2.3%	1.5%
Mexico	2.7%	1.3%
S. Korea	1.9%	-0.3%
Russia	0.6%	-0.4%

11

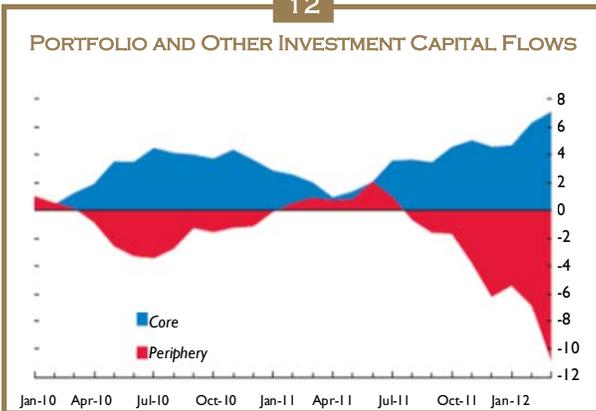
PER CAPITA CHOCOLATE CONSUMPTION AND NOBEL LAUREATES



Source: New England Journal of Medicine

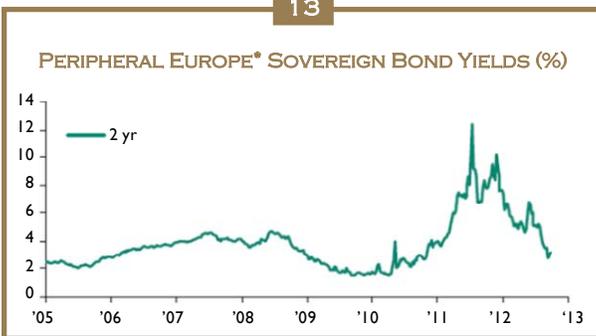


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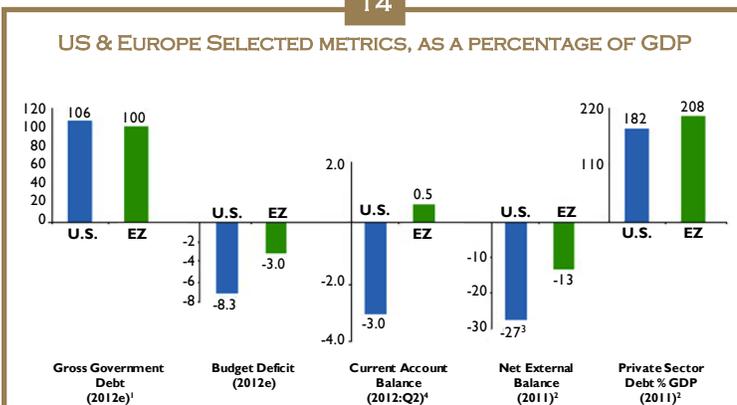
Source: Haver Analytics, and IMF staff estimates
Note: To estimate the autonomous, private-sector-driven components of total flows, flows are calculated as the sum of net portfolio and other investment flows, excluding changes in TARGET2 balances at the central bank. Core=Belgium, France, Germany and the Netherlands; periphery = Greece, Ireland, Italy, Portugal and Spain
Cumulative from December 2009, in percent of GDP in preceding years..

13



* simple average of Portugal, Italy, Ireland and Spain.
Source: BofA Merrill Lynch Global Equity Strategy, Bloomberg

14



¹ OECD Economic Outlook 91
² Source IM:
³ Through June 30, 2012. Source: Haver Analytics
⁴ Through June 30, 2012. Source: MSIM, Global Insight

from current workers. The Social Security trust fund is scheduled to run out of cash in 2033, for example, at which point benefits will be cut automatically by 25%. Additionally, lower potential growth means there is less slack in the economy than before, so the hurdle is lowered to create inflationary pressures. Higher productivity would help, but a more immediate remedy might be to increase chocolate consumption, as there is a clear correlation between per capita consumption and Nobel Laureates⁸ (Chart 11, page 6).

Progress, to a point, was apparent in Europe this past quarter. The risks of (another) banking crisis are rising as deposits are fleeing banks in the periphery (Chart 12). Outflows from Spanish banks so far this year have been the equivalent of more than 50% of GDP. So the European Central Bank (ECB) announced in September that it stood ready to purchase the bonds (all of them, if necessary) of member countries assuming they adhere to the fiscal conditions imposed by the IMF and EU (i.e., Frau Merkel). This action has been effective as yields have fallen significantly in the sovereign debt of the peripheral countries (Chart 13).

The Euro exigency is not a single crisis, but multiple challenges simultaneously. The ECB provision of liquidity has removed the immediate risks of seizure in the financial system and bank defaults. This provides some space to be

“That day will come, for the US as certainly as for Europe.”

⁸ Yes, we know that correlation is not causation, but in this case, we think it a hypothesis worth testing.
⁹ On the grounds that some children receive help from their parents and other children don't, so requiring homework is not fair. I could not make this up.



able to enact broader reforms aimed at re-balancing the significant structural differences among countries. The peripheral nations of Europe are 40% less competitive than Germany, for example, the result of faster wage growth and lower productivity over the past decade. And we'll see if M. Hollande's plan to raise the marginal income tax rate to 75%, the capital gains tax rate to 62% (applied retroactively), and to ban schools from requiring homework² will help close that gap. An alternative view is that rather than providing space for reforms to be implemented, the ECB has only delayed, and possibly exacerbated, the day of reckoning.

That day will come, for the US as certainly as for Europe. While Europe suffers from internal inconsistencies and tensions that do not exist in the US, at the aggregate level the adjustments required by the US, in its budget and current account, for example, are even greater than in Europe (Chart 14, page 7).

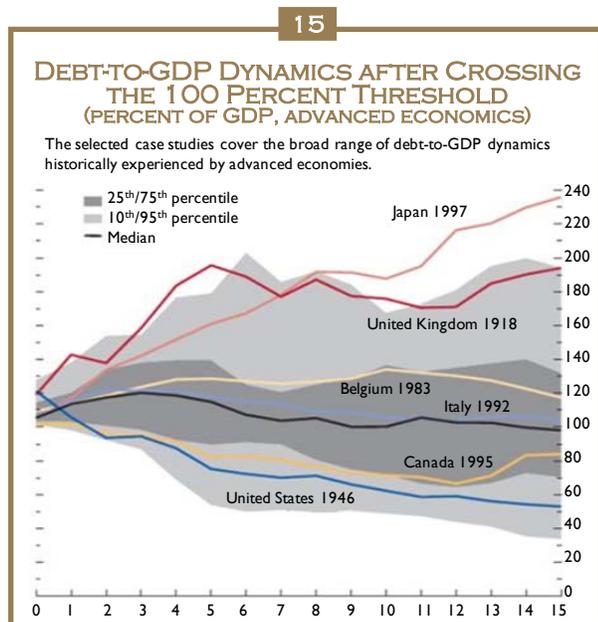
"High levels of public debt are not uncommon..."

High levels of public debt are not uncommon: the IMF cites 26 examples of debt-to-GDP ratios in excess of

100% since 1875. In these episodes, the subsequent deleveraging took many paths, some successful and some not. The US reduced its debt post-Second World War primarily through a combination of negative real interest rates and strong growth. After the First World War, UK debt increased due to the high real interest rates caused by deflation (Chart 15).

In this examination of historical deleveraging events there are four observations that offer guidance to our own efforts. One is that deleveraging takes time. In the median of these examples, debt-to-GDP was only about 10% lower after 15 years. Secondly, it helps if the rest of the world exhibits strong growth. This was the principal factor in the debt reduction that occurred in Belgium in the 1980s and Canada in the 1990s. Thirdly, an accommodative monetary policy is critically important. Real interest rates must remain low, below the growth of GDP to allow easier servicing of the debt. This is certainly the case today in the US and the UK, but it is not true in Japan, where deflation has pushed real rates to the highest in the developed world. And it is a mixed picture in Europe, where interest rates are appropriately low in Germany, the Netherlands, et.al., but punishingly high in the peripheral countries. This is one of the key challenges policymakers face in Europe: how to reconcile a single monetary policy with very divergent economic conditions and needs.

The final observation from history is that debt reduction is more successful when fiscal measures are structural rather than temporary. Belgium's success in the 1980s came from permanent spending cuts, while Canada reformed pensions and entitlement programs in the 1990s. Neither the US nor Europe has yet to begin any long-term reform of government spending. Europe created a common currency, helpful for the traveler crossing the continent, but did so without policies of fiscal transfer and the free movement of labor, as the US has. The



Source: Abbas, and others (2010); and IMF staff calculations.
Note: The horizontal axis shows the number of years after the debt-to-GDP ratio exceeds 100 percent



consequence (unintended or otherwise) is a single monetary policy inappropriately imposed on a region with vastly diverging economic conditions.

Last year, the US federal government took in about \$2.5 trillion of revenues and spent \$3.5 trillion, the fourth consecutive year spending one trillion dollars more than it has. In just these four years, the debt burden of every adult and child in the United States grew by \$17,000. Annual interest payments on the federal debt exceed \$250 billion, and in a decade will exceed \$1 trillion annually without some action.

Government policies designed to reform societal behavior have created consequences (unintended or otherwise) that are both massive and distorting. We noted last quarter of the explosion of growth in government-backed student loans, which now exceed credit card debt, initiated originally with the lofty intention of making education more affordable. But when prices are subsidized, that is, made lower artificially, the price signal that balances demand and supply is no longer effective, the specific consequence being that education costs have risen substantially faster than overall inflation. The US spends about \$750 billion on welfare programs (excluding health care), and there are approximately 40 million people identified as in poverty. Rounding those two numbers means we spend just under \$20,000 per person in poverty. The median household income is around \$50,000, so for a family of four in poverty we spend nearly \$80,000 per annum. Maybe it would make more sense just to give every family in poverty \$50,000, thereby saving \$300 billion or so.¹⁰

Herbert Stein, President Nixon's chairman of the Council of Economic Advisors, famously noted that trends that cannot continue will stop. But how they stop is critical. We can simply ride the train off the cliff, or we can take measures to avoid that calamity. More of the same thinking about these chal-

lenges is not likely to resolve these myriad issues positively. We need a new approach, which is where we turn back to that precocious boy in San Bernardino.

The family farm near Modesto was lost in the Great Depression, and with a baby boy born in 1939, whom they named Arthur, the family moved to San Bernardino to begin again. They built a mobile home park, designing the electrical and plumbing and doing most of the construction work themselves. Arthur was a good student, and graduated from nearby UC-Riverside as a chemistry major, and was then accepted into the Ph.D. program in biochemistry at Caltech. A postdoctoral job at the Salk Institute followed where he worked on the regulation of gene transcription.

By the mid-1970s, Harvard was the center of biochemistry research, led by the brilliant Walter Gilbert who, in 1980, would be awarded the Nobel Prize in Physiology for his sequencing of DNA. This is, of course, a monumental achievement, but it is a very long road from DNA sequencing to effective genetic engineering. For example, a single rat cell contains 2.5 million base-pairs of DNA, and the insulin gene contains 400 base pairs. To identify the insulin gene in this mountain of data without any clues as to where it may be hiding is not easy. Assuming this could be done, the researcher would attempt to clone that gene by inserting it into bacteria in exactly the correct way so that the cell was "tricked" into creating insulin. When we eat, the body converts food into sugar, or glucose, a form of energy. This sugar enters the bloodstream and is transported to our cells. But glucose cannot enter a cell without the hormone insulin, which unlocks the receptors in each cell, permitting glucose to move from the bloodstream into the cells. A

"...trend that cannot continue will stop. But how they stop is critical."

¹⁰ This is not a serious proposal, although you are welcome to take it seriously.

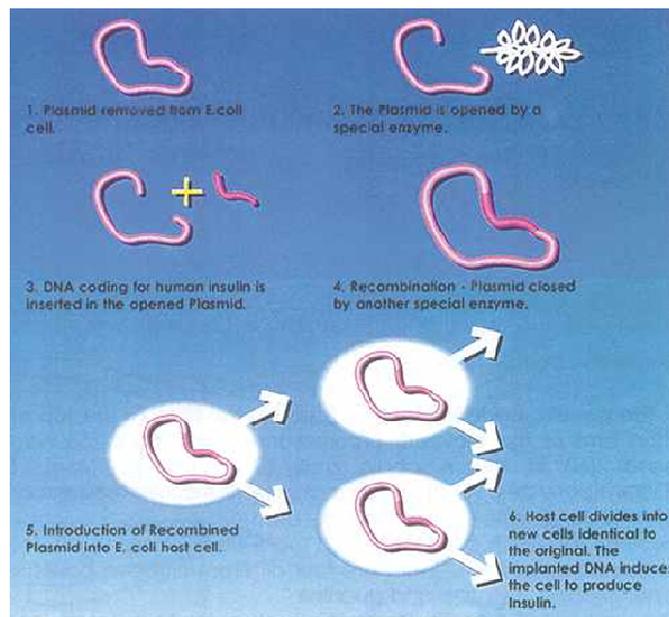


rise in our blood sugar levels triggers the pancreas to release insulin, thereby regulating our blood sugars. Without insulin, blood sugar is locked out of our cells and remains in the bloodstream. This elevated level of blood sugar, hyperglycemia, causes the symptoms of diabetes.

In 1975, Gilbert's team at Harvard announced they had found a way to make a copy of the globin gene, a protein used to make red blood cells. It was clear that they were moving rapidly to being able to replicate human insulin.

Across the country, Herb Boyer was a scientist at the rather shoddy biochemistry lab at UC-San Francisco. Boyer was one of the inventors of gene-splicing technology, and he recognized immediately the implications of the Harvard announcement that they had been able to copy a mammalian gene. He knew that despite the enormous practical challenges, the theoretical ability to synthesize human insulin was now established, and he was determined to achieve this. He formed a new company with \$100,000 from his friend, Tom Perkins,¹¹ and went out to recruit the best team of scientists he could find. Which led him to Arthur.

In early 1976, Arthur had teamed with a chemist, Keiichi Itakura, in an experiment that had nothing to do with insulin. They were trying to take an X-ray photograph of how a protein repressor attaches to DNA. The problem was that they needed to synthesize enormous amounts of DNA, a process that would take a lifetime. A random, and timely, visit by Walter Gilbert of Harvard led to a discussion, and Gilbert mentioned that they might try tying DNA tails to the T4 ligase enzyme. It worked, and they were able to synthesize DNA, they could create their gene of choice. They demonstrated that man-made DNA could be in-



Source: Novo Nordisk

serted into bacteria and become a functioning part of that organism's genetic make-up.

Back in Cambridge, the Harvard team was working toward the same goal, but using rat insulin as the basis for their experiments. In that politically charged era, some scientists at Harvard expressed ethical concerns about genetic experiments, and alerted the Cambridge City Council. A series of charged meetings and media alarm forced the Harvard team to find another lab, one with the highest level of security, to conduct their work. After months of delay, a British military installation accepted them.

The California team avoided this political controversy because it was not working with animals; their experiments were all chemical. Boyer pressed Arthur to move toward creating human insulin, but Arthur was deliberate, and said he wanted to experiment on the peptide somatostatin, to

¹¹ Founder of the legendary venture-capital firm, Kleines, Perkins, Caulfield, Byers.

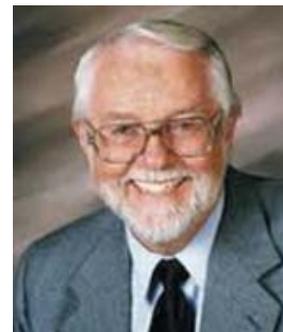


see if their method would work. They determined the genetic code of somatostatin (not an easy feat), and then attempted to attach it to the bacterium *E. coli*. It failed as they discovered that *E. coli* degraded somatostatin. So they tried a larger protein, beta-galactosidase, but the somatostatin was again rejected as a foreign substance. So Arthur had the idea to try to “hide” the hormone by inserting it in a different place in the protein. This is an extremely difficult procedural task, even for Itakura, the best chemical technician in the world. But it worked. Riggs and Itakura became the first scientists in history to build a “human” gene using widely available chemicals.

It was a short step from there to replicate their process on insulin, and on September 6, 1978, a press conference was held in Duarte, California announcing that Herb Boyer’s newly formed company, Genetic Engineering Technology, which he shortened to Genentech, and researchers at the City of Hope led by Arthur Riggs, had successfully synthesized human insulin. It would take the marketing and manufacturing prowess of Eli Lilly to bring this to market, but for the 300 million sufferers of diabetes, a safer and secure source of insulin is now available.

Arthur Riggs, Keiichi Itakura and others on the City of Hope/UCSF team prevailed against the conventional wisdom that creating a “human” gene strictly from chemicals

was impossible. Riggs’ vision and determination, and Itakura’s impeccable technique combined for one of the seminal medical breakthroughs in history. We’re pleased to note that Dr. Riggs and Dr. Itakura continue their ground-breaking research at City of Hope to this day.¹² In 2009, Genentech was bought by Roche for \$46.8 billion.



Without insulin, diabetes is a death sentence. But insulin is not a cure for this terrible disease. It is a matter of contention whether the trillions of dollars of government spending and trillions more in additional bank reserves have kept the economy functioning or laid the ground for a future calamity. But there is no dispute that we have not cured the long-term disease. That will require a new approach, with the vision and determination Arthur Riggs and his team showed us 35 years ago. 

¹² Angeles is honored to play a small part in helping City of Hope steward its investments to be able to continue to be one of the leading research institutions in the world.

Founded in 2001, Angeles Investment Advisors LLC provides investment advice to select institutions and high net worth families and individuals.



MICHAEL A. ROSEN
PRINCIPAL & CHIEF INVESTMENT OFFICER
NOVEMBER 2012

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